REMARKS

Claims 57-60 and 76-78 are pending in the subject application. No claim has been added, canceled or amended herein. Accordingly, claims 57-60 and 76-78 are still pending and under examination.

Rejection under 35 U.S.C. §103(a)

The Examiner rejected claims 57-60 and 76-78 under 35 U.S.C. §103(a) as allegedly obvious over Hori et al. (J. Biol. Chem. 1995; 270(43):25752-25761) ("Hori") in view of Miki et al. (Biochem. Biophys. Res. Commun. 1993; 196(2):984-9) ("Miki") and further in view of Parkkinen et al. (J. Bio. Chem. 1993; 268(26):19726-38) ("Parkkinen").

Applicants respectfully traverse the rejection of claims 57-60 and 76-78. In order to find the subject application obvious over Hori in view of Miki and further in view of Parkkinen, the prior art references, in combination, must teach or suggest all the elements thereof, and create both a motive to combine and a reasonable expectation of success. Hori, Miki and Parkkinen fail to do this.

The Claimed Invention

Claims 57-60 and 76-78 provide a method for identifying an agent which inhibits tumor invasion in a local cellular environment. This method comprises: (a) providing a solid support coated with amphoterin; (b) contacting the solid support with a tumor cell which expresses receptor for advanced glycation endproducts (RAGE) under appropriate cell culture conditions for cell migration and

growth; (c) admixing to the tumor cell culture of step (b) an agent to be tested; (d) determining the amount of spreading of the tumor cells on the solid support; and (e) comparing the amount of spreading of the tumor cells determined in step (d) with the amount of spreading determined in an identical tumor cell culture in the absence of the agent, wherein a decrease in the amount of spreading determined in step (d) indicates that the agent is identified as an agent which inhibits tumor invasion in the local cellular environment.

This invention is based on the *surprising discovery* that inhibiting the interaction of RAGE and amphoterin inhibits tumor invasion in a local cellular environment. Prior to applicants' discovery, there was no reasonable expectation that inhibiting the interaction of RAGE and amphoterin would succeed in inhibiting tumor invasion in a local cellular environment. The Examiner's assertion of obviousness ignores this point.

The Cited References Teach Away from the Invention

The Examiner asserts that Hori teaches a method of screening agents that inhibit the interaction of amphoterin and *neuronal* cell RAGE. The Examiner also asserts that Miki teaches that renal cell carcinomas ("RCC") express RAGE. The Examiner further asserts that Parkkinen teaches that since amphoterin is present at the leading edge of tumor cells, amphoterin mediates the path-finding functions of tumor cells and is involved in cellular invasiveness. The Examiner then asserts that after combining these references, it would have been obvious for one of ordinary skill in the art to use tumor cells in a method of screening for agents that inhibited

invasion by inhibiting the interaction of amphoterin and RAGE.

The Examiner has taken an impermissible leap in reasoning. The Examiner has in no way shown how Hori in view of Miki and further in view of Parkkinen teach or suggest applicants' invention which is based on the surprising finding discussed above. To maintain otherwise would constitute hindsight. That is, the references, according to the Examiner's understanding, individually teach (a) identification of agents that inhibit RAGE/amphoterin interaction, (b) the presence of RAGE on a carcinoma cell, and (c) amphoterin's supposed role in cellular invasiveness. In no way does the sum of these independent teachings equal a *causal* relationship between inhibiting RAGE/amphoterin interaction and inhibiting tumor invasiveness.

Indeed, the references in combination *teach away* from the invention.

The references in combination suggest a mechanism through which amphoterin engagement of RAGE was thought to suppress tumor growth, but which was later refuted by applicants in the subject application. Specifically, Parkkinen on page 19737, teaches that "[t]he adhesive properties and the ability to localize and enhance plasmin generation suggest that amphoterin may be a link between adhesive and proteolytic regulation at the leading membrane; adhesive interactions mediated by amphoterin are reversed upon complex formation with *plasminogen* and *plasminogen activators*, and plasmin generation is strongly enhanced upon the complex formation, which enhances penetration of the processes during migration." (emphasis added). To the contrary, applicants, on page 31 of the

subject application, teach that "[b]lockade of RAGE and amphoterin inhibited tumor cell invasion and migration, though proliferation, angiogenesis, *matrix attachment and cellular proteolytic (collagenolytic or plasmin) activity were unchanged.*" (emphasis added). Given the above, the Examiner cannot properly assert that at the time of the subject application's filing, amphoterin's role in tumor invasiveness, *if any* could have been speculated, was obvious and involved interaction with RAGE.

Accordingly, applicants maintain that the subject claims are not obvious over Hori in view Miki and further in view of Parkkinen, and therefore satisfy the requirements of 35 U.S.C. §103(a).

Summary

For the reasons set forth hereinabove, applicants respectfully request that the pending claims of this application be allowed.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Communication. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

10/27/03
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